REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks and amendments herein, is respectfully requested. Claims 153-154, 169 and 174-175 are amended, and claims 177-182 are added. Claims 153-154, 157-165 and 169-182 are now pending in this application.

The Non-Statutory Obviousness-Type Double Patenting Rejection

Claims 153-154, 157-165 and 169-175 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 173-194, 196-203, 205-211, and 231 of copending application Serial No. 09/754,775. As the present application and the '775 application have not yet been allowed, a terminal disclaimer is not required at this time. Should one become required, it can be requested by the Office as a condition of allowance.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 153-154, 157-165 and 169-176 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate description. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

In particular, the Examiner asserts that the specification does not describe or exemplify all agents which have reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof, and does not teach the administration of such agent(s) to a mammal, such as a mammal with decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis. The Examiner continues asserting that the specification does not provide a basis for one of skill in the art to envision any one of such agents, and no basis to predict any agent having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof.

As amended, the claims are directed to the use of TGF-beta elevating agents that have reduced estrogenic activity or DNA adduct formation relative to tamoxifen and are a structural analog of tamoxifen, a stilbene antisteroid, a 1,2 diphenylethane antisteroid, or a naphthalene antisteroid.

The specification discloses that TGF-beta elevating agents, such as tamoxifen analogs, stilbene antisteroids, 1,2-diphenylethane antisteroids and naphthalene antisteroids, with reduced estrogenic activity or DNA adduct formation relative to tamoxifen are useful to treat, inhibit or prevent cardiovascular indications. The specification also provides exemplary tamoxifen analogs, stilbene antisteroids,1,2-diphenylethane antisteroids and naphthalene antisteroids on pages 3, 7-9 and 13-15.

The Examiner is respectfully requested to consider that Applicant need not describe or exemplify every species within a genus to satisfy the written description requirement. So long as the disclosed species are representative of the genus, the written description requirement is satisfied. Thus, in view of Applicant's disclosure, one of skill in the art would understand that Applicant was in possession of the common attributes of agents useful in the claimed methods. Those attributes include, for example, structures related to tamoxifen, stilbene, 1,2-diphenylethane and naphthalene, and function, e.g., TGF-beta elevating agents with reduced estrogenic activity or DNA adduct formation relative to tamoxifen.

It is Applicant's position that the administration of compounds to mammals, and in particular, the administration of antisteroids to mammals, is known to the art. Applicant need not teach what is well-known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986).

Therefore, the claims are in compliance with the "written description" requirement of § 112, first paragraph.

Claims 153-155 and 157-168 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

The Examiner alleges that Applicant does not provide any working examples for inhibiting cardiovascular indications in a mammal by administering a TGF-beta agent that has reduced estrogenic activity relative to tamoxifen or reduced DNA adduct formation relative to tamoxifen, that the guidance in the specification towards the inhibiting of a cardiovascular indication by administering a TGF-beta agent is completely lacking, and that although the state of the art regarding treating a cardiovascular indication by administering a TGF-beta agent that has reduced estrogenic activity relative to tamoxifen or reduced DNA adduct formation relative

to tamoxifen is relatively high, the state of the art for inhibiting or preventing a cardiovascular indication by administering a TGF-beta agent in a mammal is underdeveloped. The Examiner also alleges that the instant specification does not describe or exemplify all agents which must have the property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof.

It is well-settled that there is no requirement for working examples to fulfill the requirements of 35 U.S.C. ' 112, first paragraph, if the invention is otherwise disclosed so that one of ordinary skill in the art can practice the invention without undue experimentation. In re Robins, 166 U.S.P.Q. 552 (C.C.P.A. 1970); In re Borokowski et al., 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). It is also well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Nevertheless, in Example 7 in the specification it is disclosed that mice were fed a low or high fat diet with or without tamoxifen, and vessel lesions, a characteristic of a cardiovascular disease, were measured. Tamoxifen treatment reduced the number of vessel lipid lesions (see Table 2). It is also disclosed that TGF-beta elevating agents with reduced estrogenic activity or reduced DNA adduct formation relative to tamoxifen are useful in the methods of the invention, and that in an *in vitro* system, idoxifene and tamoxifen had similar effects on vascular smooth muscle cells (Example 6). In this regard, the Examiner is requested to consider that idoxifene, toremifene and 4-iodotamoxifen are structurally related to tamoxifen, and have desirable properties, e.g., lower carcinogenicity and/or reduced estrogenicity. Moreover, idoxifene, toremifene and lasofoxifene (a naphthalene) have been shown to have beneficial cardiovascular effects (see the abstracts for Yue et al., Circ., 102:III281 (2000), Erkkola et al., Breast Can. Res. Treat., 93:277 (2005), Harvey et al., Breast, 15:142 (2005), Kusama et al., Breast Can. Res. Treat., 88:9 (2004), Kusama et al., Breast Can. Res. Treat., 88:1 (2004), Christopher et al., Eur. J. Pharmacol., 446:139 (2002), Johnston et al., Cancer Chemo. Pharmacol., 53:341 (2004), and Drugs R D., 6:56 (2005), as well as Morello et al., Crit. Rev. Oncol/Hematol., 43:63 (2002) and Vogelvang et al., Drugs, 66:191 (2006); a copy of each is enclosed herewith).

The Examiner's doubt as to "how to use" TGF-beta elevating agents within the scope of the invention must be accompanied by tangible reasons in support of the doubt. The Patent

Office must provide evidence inconsistent with the contested disclosure as it relates to the operability in the specification. In re Marzocchi et al., 169 U.S.P.Q. 367 (C.C.P.A. 1971); M.P.E.P. § 2164.03.

Moreover, if the state of the art regarding treating a cardiovascular indication by administering to a mammal a TGF-beta agent that has reduced estrogenic activity relative to tamoxifen or reduced DNA adduct formation relative to tamoxifen is relatively high, as conceded by the Examiner, it is unclear how the state of the art for inhibiting or preventing a cardiovascular indication by administering to a mammal a TGF-beta agent is underdeveloped. The Examiner is requested to consider that tamoxifen administration beginning at 8-12 weeks of age in mice fed a high fat diet resulted in a reduced number of lesions in the aorta (see Table 2). Further, the Examiner is requested to note that the claims do not recite "preventing."

With respect to disclosure of agents having reduced estrogenic activity or reduced DNA adduct formation relative to tamoxifen, the Examiner is requested to consider that methods to determine the estrogenic activity and DNA adduct forming activity of a compound were known to the art prior to Applicant's filing. See, for instance, Potter et al., Carcinogenesis, 15, 439 (1994) (of record) and Eppenberger et al., Am. J. Oncol., 14:S5 (1991) (a copy is enclosed herewith). Thus, it is Applicant's position that it is within the skill of the art, in view of Applicant's specification, to select or identify agents within the scope of the claims.

Accordingly, the specification is fully enabling.

Hence, withdrawal of the § 112(1) rejections is respectfully requested.

The 35 U.S.C. § 102 Rejection

Claims 153-154, 158, 160, 165, 169-170, and 174-175 were rejected under 35 U.S.C. § 102(b) as being anticipated by Connolly et al. (U.S. Patent No. 5,250,561). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Connolly et al. disclose tetrahydroindazole, tetracyclopentapyrazole and hexahydrocycloheptapyrazole compounds that inhibit HMG CoA reductase and cholesterol biosynthesis and their use to treat or prevent hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

To constitute anticipation, all material elements of a claim must be found in one prior art source. In re Marshall, 577 F.2d 301, 198 U.S.P.Q. 344 (C.C.P.A. 1975).

Connolly et al. do not teach or suggest the use of an agent selected or determined to be a TGF-beta elevating agent that has reduced estrogenic activity relative to tamoxifen or reduced DNA adduct formation relative to tamoxifen, and is a structural analog of tamoxifen, a stilbene antisteroid, a 1,2-diphenylethane antisteroid, or a naphthalene antisteroid.

Therefore, withdrawal of the § 102(b) rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 153-154, 157-162, 165, 169-172, and 174-176 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Morisake et al. (Atherosclerosis, 88:227 (1991)) in view of Knabbe et al. (Am. J. Clin. Oncol., 14:S15 (1991)) and further in view of Kangas (Breast Cancer Res. Treat., 16:S 3 (1990)). Claims 163 and 173 were rejected under 35 U.S.C. § 103(a) as being unpatentable Morisake et al. in view of Knabbe et al. and further in view of Kangas and further in view of Warri et al. (J. Natl. Cancer Inst., 85:1412 (1993)). Claim 164 was rejected under 35 U.S.C. § 103(a) as being unpatentable Morisake et al. in view of Knabbe et al. and further in view of Kangas and further in view of Cullinan et al. (U.S. Patent No. 5,457,113). These rejections are respectfully traversed.

Morisaki et al. report the *in vitro* treatment of mitogen-stimulated subconfluent cultures of rabbit medial- or intimal-derived aortic smooth muscle cells with purified TGF-β_1. The smooth muscle cells are derived from rabbit aortic vessels which are not traumatized by an interventional procedure. The mitogens employed by Morisaki et al. include fibroblast growth factor (FGF), smooth muscle cell-derived growth factor (SDGF), platelet-derived growth factor (PDGF), and fetal bovine serum (FBS). They disclose that the addition of greater than 10 pg/mL of purified TGF-β_1 inhibits DNA synthesis in these cultures relative to cultures treated with less than 10 pg/mL of TGF-β_1. It is also disclosed that the addition of TGF-β_1 to low density cultures of PDGF- or FBS-stimulated rabbit medial smooth muscle cells results in a lower total number of cells in these cultures relative to cultures not treated with TGF-β_1. As stated in the Abstract "TGF-beta may have different effects on cell proliferation depending on many conditions."

Morisaki et al. also compare their work with the reported conflicting results of others on the effect of TGF-β on mammalian smooth muscle cells, e.g., that TGF-β_1 stimulates proliferation in anchorage-independent smooth muscle cell cultures, and either inhibits or stimulates proliferation in confluent smooth muscle cell cultures. See page 232, Col. 1. At page 233, the authors state that: "[t]he mechanisms of the bifunctional effects of TGF-β_1 on cell proliferation depending on conditions remain to be clarified . . . ." Moreover, at page 232, Col. 2, the authors state that "there are other problems [to overcome] for TGF-β_1 to work effectively, *in vivo*."

The authors do not disclose or suggest how these "problems" can be overcome. Thus, in view of the entire teaching of Morisaki et al., one of ordinary skill in the art would not have a reasonable expectation that the administration of exogenous TGF-β *in vivo*, much less that a therapeutic agent that is not TGF-β but which increases the level of endogenous TGF-β, could effectively inhibit or treat a cardiovascular indication in a mammal, e.g., by inhibiting smooth muscle cell proliferation or lipid accumulation, or increasing plaque stability, in a diseased or traumatized vessel.

Further evidence that one of ordinary skill in the art, in possession of Morisaki et al., would not have a reasonable expectation that the administration of an agent that elevates TGF- β could inhibit or treat a cardiovascular indication in a mammal is provided by Ruoslahti et al. (WO 93/10808, of record). Ruoslahti et al. disclose that tissue pathologies characterized by a deleterious extracellular matrix accumulation, e.g., arteriosclerosis and post-angioplasty restenosis, can be treated by contacting the tissue with an agent that suppresses the activity of TGF-β, e.g., an anti-TGF- β antibody.

The Examiner asserts that, based on the paragraph beginning on page 227 up to line 6 on page 228, column 2, lines 5-7 on page 229, and lines 1-3 in the second paragraph in the discussion section of Morisaki et al. (which is on page 232), the reference teaches that TGF-β is useful in the treatment of atherosclerosis because it has been shown to inhibit the proliferation of smooth muscle cells along the blood vessel, which is the cause of atherosclerosis.

However, the cited portions of Morisaki et al. disclose that TGF-β_1 may play an important role in the development of atherosclerosis, TGF-β_1 inhibits cell proliferation of quiescent subconfluent smooth muscle cells *in vitro* irrespective of the cell phenotype or the

growth factor inducing proliferation, and the factors underlying the discrepancy between their findings and those of Goodman et al. are unknown. Thus, contrary to the Examiner's assertions, the cited portions of Morisaki et al. do not disclose that TGF-β administration inhibits smooth muscle cells along the blood vessel. Nor does Morisaki et al. disclose selecting or determining agents that elevate TGF-beta and are structural analogs of tamoxifen, stilbene antisteroids, 1,2 diphenylethane antisteroids, or naphthalene antisteroids, and using those agents to treat cardiovascular indications.

Knabbe et al. report that that addition of droloxifene, tamoxifen and toremifene to MCF-7 breast cancer cells *in vitro*, induces TGF-β. It is also disclosed that droloxifene is a more effective inducer of TGF-β and a more potent growth inhibitor for estrogen responsive human breast cancer cells than tamoxifen and toremifene *in vitro*.

Kangas reviews the pharmacological properties, safety, pharmacokinetics and clinical developments for toremifene as a breast cancer chemotherapeutic.

Therefore, Knabbe et al. and Kangas do not remedy the deficiencies in Morisaki et al.

Further, it is believed that the addition of Warri et al. or Cullinan et al. does not remedy the deficiencies of Morisaki et al., Knabbe et al. and Kangas individually or in combination with each other.

Accordingly, withdrawal of the § 103(a) rejection is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date December 2, 2008 By

Janet E. Embretson
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 2nd day of December, 2008.

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Signature